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EXAMINER	
TURNER, SHARON L	

ART UNIT	PAPER NUMBER
1647	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/870,932	WU ET AL.	
	Examiner	Art Unit	
	Sharon L. Turner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *147-210* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *147-210* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The communications of 2-4-04 and 3-22-04 and 7-19-04 have been entered into the record and have been fully considered.

2. New claims 147-210 are pending.

Election/Restrictions

3. Claims 147-210 are generic to a plurality of disclosed patentably distinct species comprising antibodies or antibody fragments that inhibit binding of chemokines a) MIP-1α, b) MIP-1β or c) RANTES to the human CCR5 receptor. Applicant is required under 35 U.S.C. 121 to elect a single disclosed species of chemokine, i.e., either a) MIP-1α, b) MIP-1β or c) RANTES, even though this requirement is traversed.

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

This requirement is deemed necessary for examination purposes due to the introduction of the new limitations directed toward the specificity of the antibodies and antibody fragments to the different chemokines and arguments of record that the various chemokines are subject to different specific receptor binding parameters and hence the antibodies and antigen binding fragments thereof provide for different regional antibody binding/inhibiting specificity.

Applicant's election with traverse of RANTES in the reply filed on 7-19-04 is acknowledged. The traversal is on the ground(s) that the claims are drawn to antibodies and antibody fragments that bind CCR5 and not the different chemokines, that no arguments have been made that state the chemokines are subject to different specific receptor binding parameters or binding/inhibiting specificity, that the chemokine limitations are not new limitations and were previously searched and considered by the Examiner.

These arguments have been fully considered and are found to be persuasive. The restriction requirement is therefore withdrawn and claims 147-210 are pending and are under examination. However, Applicant's are put on notice that distinction of the antibodies with respect to binding specificity may require reinstatement of the restriction (species) election requirement.

Double Patenting

4. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

5. Claims 147-210 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-36 of U.S. Patent No. 6,528,625. Although the conflicting claims are not identical, they are not patentably distinct from each other because instant claims are rendered obvious in view of the '625 patented claims directed to the HB-12366 (2D7) antibody, antigen binding fragment, antibody producing hybridoma, compositions and test kit with properties including all limitations as instantly recited. The disclosure of the species renders obvious the instant generic recitations.

While Applicants have previously noted that a terminal disclaimer would be submitted, this is the first notification of rejection over the newly recited claims.

Priority

6. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

As set forth in the new matter rejection below, claims 147-210 are directed to a subgenus of antibodies not supported by the specification or within the noted priority documents as originally filed. In the amendment of 2-4-04, Applicants state that no new

matter is added and that support for the newly recited claims may be found within the specification at p. 11, lines 18-19; p. 12, lines 1-2; and page 59, line 24 through page 60, line 23. However, particular support for the new claim recitations is not found at these cited passages. Support is noted for antibodies as directed at p. 11-12, paragraph spanning. Further, support is noted for 5C7 as at p. 60. However, the claims are not directed to the genus of antibodies contemplated/supported in the specification as originally filed.

In particular, the claims are directed to a subgenus of CCR5 antibodies which binds "*human* CCR5" wherein the antibody or fragment is further capable of inhibiting binding of *chemokines* (MIP-1α, MIP-1β and RANTES) *or combination thereof*, to human CCR5 and which *inhibits one or more functions associated with binding of a chemokine to the receptor*." Yet these limitations differ from the disclosure as directed at p. 11-12, to antibodies or antigen binding fragments that inhibit binding of a "*ligand*" and "*one or more functions mediated by CCR5 in response to the ligand.*" Moreover, specific support for the further subgenus of these antibodies that are chimeric, human, humanized, binds the second extracelluar loop and inhibits HIV infection are not specifically noted.

Therefore the effective filing date with respect to instant claims is the instant filing date of May 30, 2001. Traversal of the priority determination should note where all claim limitations are specifically supported within Applicant's specification and the noted priority documents for the earliest effective filing date sought.

Claim Objections

7. Claims 148, 152, 159, 162, 169, 173, 180, 183, 190, 194 and 204 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The claims do not further limit the parent or independent claims because the parent or independent claims already specify that the antibody or antigen binding fragment binds/has specificity for human chemokine receptor 5.

Claim Rejections - 35 USC § 101

8. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

9. Claims 147-210 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claims do not reflect isolation, or the hand of man and read on a naturally produced product of nature. The term 'isolated' should be inserted so as to recite "An isolated antibody or antigen binding fragment thereof...".

Claim Rejections - 35 USC § 112

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 147-210 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to

one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection as the claims are now directed to a subgenus which constitutes a departure from the original specification.

Claims 147-210 are directed to a subgenus of antibodies not supported by the specification as originally filed. In the amendment of 2-4-04, Applicants state that no new matter is added and that support for the newly recited claims may be found within the specification at p. 11, lines 18-19; p. 12, lines 1-2; and page 59, line 24 through page 60, line 23. However, particular support for the new claim recitations is not found at these cited passages. Support is noted for antibodies as directed at p. 11-12, paragraph spanning. Further, support is noted for 5C7 as at p. 60. However, the claims are not directed to the genus of antibodies contemplated/supported in the specification as originally filed.

In particular, the instant claims are directed to a subgenus of CCR5 antibodies which binds "*human* CCR5" wherein the antibody or fragment is further capable of inhibiting binding of *chemokines* (MIP-1α, MIP-1β and RANTES) *or combination thereof*, to human CCR5 and which *inhibits one or more functions associated with binding of a chemokine to the receptor*." Yet these limitations differ from the disclosure as directed at p. 11-12, to antibodies or antigen binding fragments that inhibit binding of a "*ligand*" and "*one or more functions mediated by CCR5 in response to the ligand.*" Moreover, specific support for the further subgenus of these antibodies that are chimeric, human, humanized, binds the second extracelluar loop and inhibits HIV infection are not

specifically noted. Applicant's reliance on a generic disclosure and possibly a single or limited species does not provide sufficient direction and guidance to the features currently claimed. It is noted that a generic or a sub-generic disclosure cannot support a species unless the species is specifically described. It cannot be said that a subgenus is necessarily described by a genus encompassing it and a species upon which it reads. See In re Smith 173 USPQ 679, 683 (CCPA 1972) and MPEP 2163.05.

11. Claims 147-210 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for antibodies or antigen binding fragments thereof that inhibit binding of chemokine ligands MIP-1α, MIP-1β and RANTES to human CCR5, and for the specific deposits of antibodies 5C7 and 2D7 as noted in the deposits; does not reasonably provide enablement for antibodies with such functional recitations specific to chemokine binding, functions associated with binding of a chemokine to the receptor to antibodies or to specific epitope regions such as the second extracellular loop. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The grounds of rejection are as set forth in the Office action of Paper No. 14, 4/15/03 and are as set forth herein with respect to the amended claims. Amendment to "human CCR5" has obviated the grounds of rejection with respect to the recitation of any "mammalian" CCR5. However, the aforementioned claims remain drawn generically to any chemokine capable of binding human CCR5.

As previously set forth, only chemokines MIP-1α, MIP-1β and RANTES are disclosed as binding human CCR5.

Applicants argue in the response of 3-22-04 that the specification as filed enabled the artisan to make and use the claimed antibodies without undue experimentation. Applicants submit that only routine experimentation would be required given the Examples 1 and 4, p. 3, 51-52 and 62-63, and that the chemokine family is well known in the art, specification p. 1-3, with reference to Zlotnik and Yoshie, teching a new classification system for chemokine members.

Applicants arguments filed 7-19-04 have been fully considered but are not persuasive. The rejection of record may be found in full in Paper No. 14. For the reasons of record, the disclosure of a single species of CCR5 (human) and three chemokines bound by human CCR5 (i.e., MIP-1α, M1P-1β, and RANTES) does not appear to provide sufficient guidance to direct a person of skill in the art in how to make and use an antibody which inhibits binding of any "chemokine" to a CCR5 protein of any mammalian origin. The Examiner acknowledges that Zlotnlk and Yoshie teach a new classification system, but their summary of what is known regarding the binding of multiple chemokines to any given receptor underscores that the skilled artisan could not reasonably predict what other newly identified (or unidentified, considering the time of the invention and this post-filing date reference) chemokines would also bind human CCR5.

The claims as directed to inhibiting binding of any "chemokine" to the receptor are akin to a single means claim, i.e., where a means recitation does not appear in

combination with another recited element of means. Such recitations are subject to an undue breadth rejection under 35 USC 112, first paragraph because the specification at most would only disclose those means known to the inventor at the time of the invention, see in particular MPEP 2164.08(a). Here no other chemokines capable of such binding are known or disclosed other than MIP-1α, MIP-1β and RANTES.

Further, as to the new recitations directed to "inhibit(ing) HIV infection," the specification teaches that specific monoclonal antibodies with epitope specificity within the region of the amino terminus or second extracellular loop were capable of inhibiting binding and entry of HIV, see in particular pp. 60-67, especially pp. 65-67. In contrast, only antibodies with epitopes specific to the second extracellular loop were capable of inhibiting binding of chemokines MIP-1α, MIP-1β and RANTES to human CCR5.

Instant claims are directed generically to antibodies or antigen binding fragments that bind to human CCR5 and inhibit binding of a chemokine to the receptor, inhibits one or more functions associated with binding of the chemokine to the receptor and inhibits HIV infection. Accordingly, Applicants have chosen to define the antibodies and antigen binding fragments solely by functional properties of the 2D7 species. While an antibody molecule imparts some particular structure, for example heavy and light chains, the epitope specificity of the antibody and binding properties are directed by the antibody structure within the variable binding domain of the molecule. However, only the 2D7 antibody with epitope specificity within the second extracelluar loop is disclosed as exhibiting the claimed characteristics, i.e., for inhibition of chemokines MIP-1α, MIP-

1β, RANTES and HIV binding as well as inhibition of one or more functions associated with binding of the chemokine to the receptor and inhibition of HIV entry.

Yet the claims do not delineate these apparent structural constraints of the antibody variable domains. Further the claims fail to recite the epitope specificity apparently required for conveying these properties, i.e., specificity for the second extracellular loop. No other structural, functional or epitope specificity guidance is provided. Thus, absent further direction, the artisan cannot make and use the antibodies with the recited functional properties without further undue experimentation to define those portions conveying the functional constraints and/or further characterization of any other epitopes capable of sharing the recited functional characteristics.

Further, as to claim 185, a composition is recited, yet only an antibody or antigen binding fragment is provided. The composition is absent any other element. Thus, the claim does not direct suitable for a composition and therefore is non-enabling as to the preamble recitation.

Finally, the Examiner notes that Applicant's arguments in traverse of the art rejections of record support the aforementioned scope of enablement rejection. In particular, applicants argue for example that Olson supports that not all antibodies have the function of inhibiting chemokine binding and one or more functions associated with chemokine binding. To the extent that applicants argue the prior art as non-enabling, so to does Olson support non-enablement within the full scope of the claims absent

specific guidance as to those structural and functional characteristics of a genus of antibodies capable of providing the recited functions.

It is noted that the specifics of the deposit are enabled as set forth in the preamble of this rejection. However, the claims depend from a rejected base claim and thus are rejected herein as being dependent thereon. To the extent that the deposits refer to a preamble that is not fully enabled and does not suitably describe the deposits, rejection is maintained over the accession numbers. While applicants may not rewrite the claims with all limitations of the independent claim to expedite allowance, Applicants may rewrite an independent claim directed to the deposits or rewrite the preamble such that it is in scope with the disclosure.

Thus in view of the extensive breadth of the instant claims, the presence of working examples that are limited to a single antibody 2D7 capable of inhibiting binding of the three known chemokine ligands of human CCR5, the unpredictability associated with identifying other chemokines that bind human CCR5 with the required functional constraints and the absence of guidance as to the generic characteristics of such antibodies and epitope specificity for the second extracellular loop includig for HIV binding and entry, not necessarily infection; the experimentation left to those skilled in the art to make and use the antibodies as currently broadly recited is unnecessarily, and improperly, extensive and-undue. The rejection is maintained for the reasons of record set forth in full in Paper No. 14 and as further noted herein.

12. Claims 147-210 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The grounds of rejection are as set forth in the Office action of Paper No. 14, 4/15/03 and as set forth herein with respect to the claim amendments. Amendment to "human CCR5" has obviated the grounds of rejection with respect to the recitation of any "mammalian" CCR5. However, the aforementioned claims are drawn generically to any chemokine capable of binding human CCR5 and inhibiting one or more functions associated with binding of the chemokine to the receptor, to the second extracellular loop and to inhbiting HIV infection. ~~domainbinding of a chemokine to~~. As previously set forth, only chemokines MIP-1α, MIP-1β and RANTES are disclosed as binding human CCR5.

Applicants argue in the response of 7-19-04 that disclosure of MIP-1α, MIP-1β and RANTES binding to human CCR5 constitutes a sufficient number of species to meet the written description requirement.

Applicants arguments filed 7-19-04 have been fully considered but are not persuasive. As previously noted, while the Examiner acknowledges that the CC chemokine family shares some common structural motifs, the evidence of record establishes that this shared family structure does not convey the functional activities of CCR5 specific binding since not all CC chemokines (as identified) bind CCR5. In addition, it is again noted that the instant claims encompass antibodies that inhibit

binding of any chemokine to human CCR5 and any one or more functions associated with binding. Applicants have not described what structural attributes make any chemokine capable of binding human CCR5 or what functions are associated. Nor have they provided the artisan with any means to immediately envision or predict from all chemokines, those which would be capable of binding human CCR5 and exhibiting the noted functional characteristics. Absent a sufficient description of the receptor-ligand pairs, or a means for immediately recognizing those chemokines that readily bind, there is not adequate written description support of the genus as directed to antibodies or antigen binding fragments that inhibit binding of any chemokine to the human CCR5 receptor and further that provides for inhibition of one or more ill described functions associated with binding of the chemokines to the receptor.

Moreover, the specification teaches the apparent requirement for the antibody or antigen binding fragment to be specific to the second extracellular loop in order for the antibodies to provide the noted functional characteristics, yet such is not an element of the claims, nor is there sufficient support to denote that this division is a further sub-species or sub-genus readily contemplated by Applicnats.

Further, as to the new recitations directed to "inhibit(ing) HIV infection," the specification teaches that monoclonal antibodies to the amino terminus or second extracellular loop were capable of inhibiting HIV binding and entry, see in particular pp. 60-67, especially pp. 65-67. In contrast, only antibodies to the second extracellular loop of CCR5 were capable of inhibiting binding of chemokines MIP-1α, MIP-1β and

RANTES to human CCR5 and inhbiting HIV binding and entry. These specifics are not limitations of the claims.

Accordingly, Applicants have chosen to define the antibodies and antigen binding fragments solely by functional characteristics without structural requirements that direct those characteristics. While an antibody molecule imparts some particular structure, for example heavy and light chains, the specificity of antibody binding is dependent upon the structure of the variable domain of the antibody molecule. Only antibodies with specificity to the second extracelluar loop are disclosed as exhibiting the claimed characteristics, i.e., for inhibition of chemokines MIP-1α, MIP-1β, RANTES and HIV binding as well as HIV entry.

Yet the claims do not delineate these apparent structural constraints of the antibody variable domains. Further the claims fail to recite the epitope specificity apparently required for conveying these properties, i.e., specificity for the second extracellular loop. No other structural, functional or epitope specificity guidance is provided. Without such description the artisan cannot immediately envisage those antibodies capable of meeting the claim recitations and adequate written description support is not provided for a genus.

Finally, the Examiner notes that Applicant's arguments in traverse of the art rejections of record support the aforementioned written description rejection. In particular, Applicants argue that Olson evidences that not all antibodies have the function of inhibiting chemokine binding and one or more functions associated with chemokine binding. To the extent that applicants argue the prior art as not-sufficiently

described (for lacking particular description of the properties), so to is Applicant's specification lacking in description of those specific structural characteristics providing for the recited functional constraints. Thus, the rejection is maintained for the same reasons of record as set forth in the Office Action of 4/15/04, Paper No. 14 and as noted herein.

Claim Rejections - 35 USC § 102

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

14. Claims 147-210 are rejected under 35 U.S.C. 102 (b) and 102(e) as being anticipated by Li et al. (US Pat. No. 6,025,154, Feb. 15, 2000, IDS AE, see entire document) as evidenced by Wu et al. (J. Exp. Med. 1997; 186(8): 1373-1381, October, IDS #AS4), Samson et al., J. Biol Chem., Oct. 1997, 272(40):24934-41, Raport et al., 1996 IDS Reference AW and Combadiere et al., 1996 IDS Reference AT3, and Atchison, IDS Reference AZ5. The grounds of rejection are as set forth in the Office Action of 1/10/03, Paper No. 14 and as further set forth herein.

Applicants argue in the response of 7-19-04 that the Li reference is not sufficiently enabled or described because the reference does not disclose any CCR5

Applicants argue in the response of 7-19-04 that the Li reference is not sufficiently enabled or described because the reference does not disclose any CCR5 ligands, does not exemplify the screening assays or actually make the antibodies. Applicants further argue that the limitations of the claims are not necessarily provided within the disclosure of Li. Further Wu is said not to supplement in that it does not establish that the Li antibodies would necessarily inhibit binding of one or more functions of the chemokines of CCR5 (MIP-1α, MIP-1β and RANTES) with reference to Olson. Applicants thus submit that the recitations of specific chemokines and binding to the second extracellular loop teach over the prior art.

Applicants arguments have been fully considered but are not persuasive. As previously noted, Olson unlike Li, did not select for antagonists (antibodies) inhibiting chemokine binding but rather antibodies that blocked HIV mediated fusion, see in particular p. 4147. Such identified antibodies were subsequently tested for their effect on chemokine binding. Thus, Olson is directed to a different screen and does not teach away from the screening taught by Li. The selection of chemokines MIP-1α, MIP-1β and RANTES that bind CCR5 is not an inventive contribution as suggested by applicants. Such ligands were already recognized as ligands binding CCR5 and mediating receptor signaling, see in particular Raport et al., 1996 IDS Reference AW and Combadiere et al., 1996 IDS Reference AT3, for example. The Li reference teaches to screen for antibodies that inhibit chemokine binding and the functions of chemokine binding at the receptor. Thus, the Li reference does teach and is enabling for the screening of the specifically known ligands as well as their receptor functions as

established in the art. Moreover, Raport notes that, "this same combination of chemokines has recently been shown to potently inhibit human immunodeficiency virus replication in human peripheral blood leukocytes," and others citing the N-terminus and second extracellular loop as important in mediating HIV infection, and in part separable from chemokine binding (with reference to the N-terminus), see in particular Atchison, IDS Reference AZ5. Further, that the Li chemokine binding region is within the second extracellular loop is established as via Wu, and moreover via Samson, J. Biol Chem., Oct. 1997, 272(40):24934-41, now of record. Accordingly, the screening assay of Li would necessarily result in the identification of antibodies specific to the second extracellular loop, i.e., the chemokine binding and signaling site. That this site is also evidenced as the major co-receptor allowing infection of HIV is further evidenced as noted via Samson and Atchison. Hence, the screening assay of Li would further necessarily identify antibodies capable of inhibiting infection of HIV as the ligand binding site of the second extracellular loop is critical to HIV infection. Both properties are evidenced as mapping to the same site, i.e., within the second extracellular loop, see in particular Wu, Atchison, Samson, Raport and Combardiere. To the extent that the parent claims are rejected, so to must the noted deposit absent identifying characteristics that would teach over the prior art. Thus, the rejection is maintained with further evidence as to the newly directed functional properties.

15. Claims 147-210 are rejected under 35 U.S.C. 102(b) and 102(e) as being anticipated by Hoxie (US Pat &0. 5,994,515, Nov. 30, 1999, IDS AB, see entire

dpcument) as evidenced by Olson et al..(J. Virol., 1999; 73:4145-4151, IDS #AW5) and Wu et al. (J. Exp. Med. 1997; 186(8):1373-1381, IDS #AS4). The grounds of rejection are as set forth in the Office Action of 1/10/03, Paper No. 14 and as further reiterated herein.

Applicants argue in the response of 7-19-04 that Hoxie does not necessarily provide the recited antibodies or teach the noted limitations. Applicants argue that Hoxie's experimentation is to CXCR4 and not CCR5. In particular, Applicant's position is that the antiviral antibodies of Hoxie would not necessarily exhibit the inhibition of chemokine binding or one or more functions associated with binding. Applicants point to the teachings of Atchison and Gosling as to partially dissociable activities within CCR5 for HIV infection and chemokine signaling. Applicants assert that the Olson teachings do not mean that an antibody that inhibits HIV entry as disclosed by Hoxie would necessarily have the properties of instant claims.

Applicant's arguments filed 7-19-04 have been fully considered but are not persuasive. Hoxie's method includes screening for antibodies capable of inhibiting HIV infection. Olson notes the most effective antibodies identified via such selection criteria are those that bind at the second extracellular loop, within the chemokine ligand binding domain and which inhibit calcium flux (receptor function). Thus, while it is true that other antibodies may be identified using the inhibition of envelope fusion and entry as selection criteria. Nevertheless, Olson evidences that the clamed antibodies are necessarily provided using such screening techniques as the antibodies were subsequently identified as antibodies capable of inhibiting HIV infection, inhbiting

chemokine binding and receptor function. In particular, the antibodies that are the most effective at inhibiting HIV infection and are necessarily selected based upon this selection criteria, are noted to be specific to the ligand binding site and to inhibit calcium influx (receptor function). The reference is fully enabled for that selection criteria for which it teaches and the human CCR5 antibodies that share these characteristics. To the extent that the parent claims are rejected, so to must the noted deposit absent identifying characteristics that would teach over the prior art. Thus, rejection is maintained.

16. Claims 147-210 are rejected under 35 U.S.C. 102(b) and 102(e) as being anticipated by Littman et al. (US Pat. 5,939,320, Aug. 17, 1999, IDS # AA, see entire document) as evidenced by Olson et al., (J. Virol., 1999; 73:4145-4155, IDS.#AW5) and Wu et al. (J. Exp. Med. 1997; 186(8):1373-1381, IDS #AS4). The grounds of rejection are as set forth in the Office Action of 1/10/03, Paper No. 14 and as further reiterated herein.

Applicants argue in the response of 7-19-04 essentially as noted above, that Littman does not necessarily provide the recited antibodies or teach the noted limitations of the claims as to chemokine binding and receptor function. In particular, Applicant's position is that the antiviral antibodies of Littman would not necessarily exhibit the inhibiton of chemokine binding or one or more functions associated with binding. Applicants assert that the Wu and Olson teachings do not mean that an antibody that inhibits HIV entry as disclosed by Littman would necessarily have the properties of instant claims.

Applicnant's arguments filed 7-19-04 have been fully considered but are not persuasive. Littman's method is for screening for antibodies capable of inhibiting HIV infection. Olson notes the most effective antibodies identified via such selection are those that bind at the second extracellular loop, within the chemokine ligand binding domain and which inhibit calcium flux (receptor function). Thus, while it is true that other antibodies may have been identified using such selection criteria, nevertheless, Olson evidences that the antibodies recited are necessarily provided. In particular, these are the antibodies that are the most effective at inhibiting HIV infection and would necessarily be selected and identified based upon the noted selection criteria. To the extent that the parent claims are rejected, so to must the noted deposit absent identifying characteristics that would teach over the prior art. Thus, rejection is maintained.

Claim Rejections - 35 USC § 103

17. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

18. Claims 147-210 are rejeçted under 35 U.S.C. 103(a) as being unpatentable over Chuntharapai et al. (US Pat. No. 5,543,503, IDS Ref. AD) in view of either Rapprt et al J. Biol. Chem. 271:11161.17166 1996, IDS Ref. AW), Samson et al. (Biochem. 35:3362-3367 1996, IDS Ref. AV), or Combadiere et. al. (J. Leukoc.,Biöl. 60:147-152 1996, IDS Ref. AT)), as evidenced by Wu et al. (J. Exp. Med. 1997; 186(8):1373.-1381,

IDS Ref. AS4). The grounds of rejection are as set forth in the Office Action of 1/10/03, Paper No. 14 and as further reiterated herein.

Applicants argue in the response of 7-19-04 that the prior art does not provide the suggestion or establish reasonable expectation of success. Applicants submit that the combination fails to teach an anti-CCR5 antibody which inhibits chemokine binding and inhibition of receptor function. Applicants argue that the prior art is not directed to the same antibodies claimed and that the declaration of Walter Newman as to the difficulty in obtaining antibodies to CCR5 establishes no expectation of success.

Applicants arguments filed 7-19-04 have been fully considered but are not persuasive as Chuntharapai notes the suggestion of making antibodies specific for a chemokine family receptor such that the antibodies bind and inhibit receptor function. The human CCR5 receptor and chemokine ligands were known in the art as well as suitable assays for assessing binding and receptor function. The suggestion and means for screening are suitably provided and the making of such antibodies, while requiring extensive experimentation does not involve experimentation that is undue or not well established in the art. Thus, both suggestion and reasonable expectation of success are provided. To the extent that the parent claims are rejected, so to must the noted deposit absent identifying characteristics that would teach over the prior art. Thus, rejection is maintained.

19. Claims 147-210 are rejeçted under 35 U.S.C. 103(a) as being unpatentable over Chuntharapai et al. (US Pat. No. 5,543,503, IDS Ref. AD) in view of either Rapprt et al

J. Biol. Chem. 271:11161.17166 1996, IDS Ref. AW), Samson et al. (Biochem. 35:3362-3367 1996, IDS Ref. AV), or Combadiere et. al. (J. Leukoc.,Biöl. 60:147-152 1996, IDS Ref. AT)), as evidenced by Wu et al. (J. Exp. Med. 1997; 186(8):1373.-1381, IDS Ref. AS4) further in view of Ramakrishnan et al., (US Pat. No. 5,817,310). The grounds of rejection are as set forth in the Office Action of 1/10/03, Paper No. 14 and as further reiterated herein.

Applicants argue in the response of 7-19-04 that the prior art does not provide the suggestion or establish reasonable expectation of success. Applicants submit that the combination fails to teach an anti-CCR5 antibody which inhibits chemokine binding and inhibition of receptor function. Applicants argue that the prior art is not directed to the same antibodies claimed and that the declaration of Walter Newman as to the difficulty in obtaining antibodies to CCR5 establishes no expectation of success. Applicants further argue with respect to Ramakrishnan that the teachings as to chimeric or humanized antibodies fail to remedy the deficiencies of the aforementioned references.

Applicants arguments filed 7-19-04 have been fully considered but are not persuasive as Chuntharapai notes the suggestion of making antibodies specific for a chemokine family receptor such that the antibodies bind and inhibit receptor function. The human CCR5 receptor and chemokine ligands were known in the art as well as suitable assays for assessing binding and receptor function. The suggestion and means for screening are suitably provided and the making of such antibodies, while requiring extensive experimentation does not involve experimentation that is undue or

not well established in the art. Thus, both suggestion and reasonable expectation of success are provided. Ramakrishnan further provides the suggestion and means for making suitable chimeric and humnanized antibodies. The suggestion is provided as well as expectation of success. To the extent that the parent claims are rejected, so to must the noted deposit absent identifying characteristics that would teach over the prior art. Thus, rejection is maintained.

Conclusion

20. No claims are allowed.

21. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should

you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharon L. Turner, Ph.D. whose telephone number is (571) 272-0894. The examiner can normally be reached on Monday-Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached at (571) 272-0961.

9-29-04

SHARON L. TURNER, PH.D.
PATENT EXAMINER

Sharon L. Turner, Ph.D.
September 29, 2004